LEARNING TO SEE AGAIN: BIOLOGICAL CONSTRAINTS ON CORTICAL PLASTICITY AND THE IMPLICATIONS FOR SIGHT RESTORATION TECHNOLOGIES

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1. ABSTRACT

The bionic eye – so long a dream of the future – is finally becoming a reality with retinal prostheses available to patients in the US and Europe. However, clinical experience with these implants has made it apparent that the vision restored by these devices differs substantially from normal sight. Consequently, the ability to learn to make use of this abnormal retinal input plays a critical role in whether or not some functional vision is successfully restored. The goal of the present review is to summarize the vast basic science literature on developmental and adult cortical plasticity with an emphasis on how this literature might relate to the field of sight recovery. We begin with formal definitions of cortical plasticity and perceptual learning. We then describe what is known, and what is unknown, about visual plasticity across the hierarchy of brain regions involved in visual processing, and across different stages of life. We close by discussing what is known about brain plasticity in sight restoration patients and discuss biological mechanisms that could be harnessed in future technologies to improve visual learning in these patients.

2. INTRODUCTION

The field of sight restoration has made dramatic progress in the last five years. The Argus II device (epiretinal, Second Sight Medical Products Inc. Rizzo et al. 2014) as well as the Alpha-IMS system (subretinal, Retina Implant AG, Stingl et al. 2015) recently completed clinical trials and were approved for commercial sale in the US and Europe, respectively. Several other electronic vision implants have either started or are planning to start clinical trials in the near future. These include the IRIS II (epiretinal, Pixium Vision, Hornig et al. 2017), PRIMA (subretinal, Stanford University, Mathieson et al. 2012), as well as devices by the Bionic Vision Australia consortium (suprachoroidal, Saunders et al. 2014), Nidek Co. Ltd. (suprachoroidal, Fujikado et al. 2011) and Nano Retina (epiretinal). At the same time, sight recovery technologies based on optogenetics and gene therapies are also making considerable strides; over a dozen human gene therapy trials are underway (Petrs-Silva and Linden 2014), and optogenetic clinical trials will likely begin within the next two years (Busskamp et al. 2012). Within a decade, many individuals suffering

from blindness are likely to be offered a wide range of options for sight restoration that depend on widely different technologies (Fine et al. 2015, Ghezzi 2015).

Clinical trials suggest that visual prostheses can provide visual information that is useful in daily life in some patients, enabling these individuals to perform simple object localization, motion discrimination, and letter identification tasks (Zrenner et al. 2011, Humayun et al. 2012, Stingl et al. 2013). However, these reports also highlight the limitations of current devices. Only a handful of patients show performance close to the theoretical limits that would be expected if performance were limited by the spacing and density of the electrodes. Insights from psychophysical experiments and theoretical considerations (reviewed in Fine and Boynton 2015) suggest that this may be due to interactions between implant electronics and the underlying neurophysiology of the retina that result in significant spatiotemporal distortions that include, for example, visual "comets" in epiretinal prostheses and motion streaks in optogenetic devices, Figure 1.

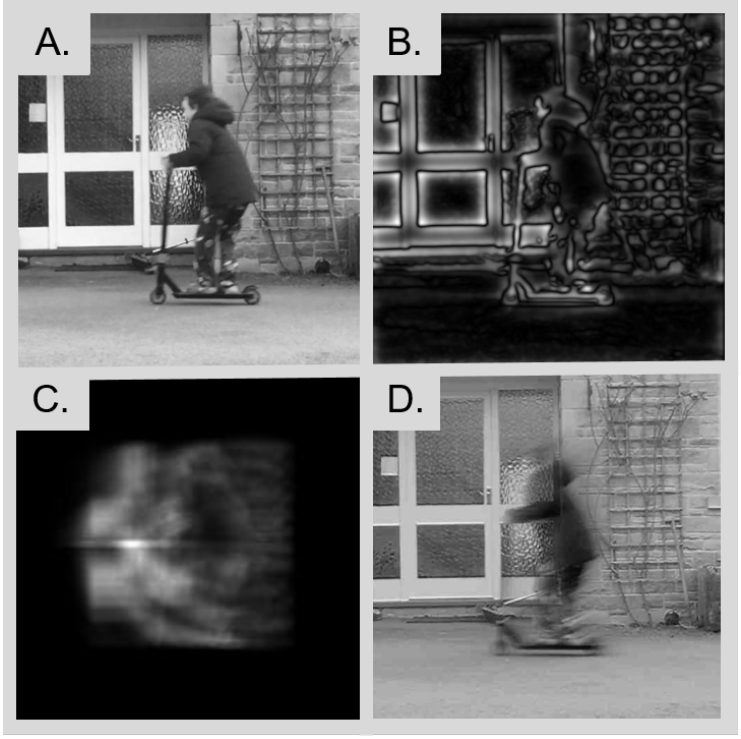

Figure 1. Example models of perceptual experience for sight recovery. All images are based on the central 12° region of a movie and a 1000x1000 array (A.) original image. (B.) Sub-retinal electrical stimulation. This particular simulation is based on simultaneously stimulating ON and OFF pathways with no axonal stimulation. (C.) Epiretinal electrical stimulation. This particular simulation is based on simultaneously stimulating ON and OFF pathways with axonal stimulation. Stimulation of axons results in visual 'comets'. (D.) Optogenetic stimulation. Based on a model of simulating ON-pathways with an optogenetic protein with temporal dynamics based on ReaChR (Sengupta et al. 2016). Motion streaks are the result of the sluggish temporal dynamics of ReaChR. Modified figure based on Fine and Boynton (2015).

Clinical experience with these implants has made it apparent that the vision restored by these devices differs substantially from normal sight. Consequently, the ability to learn to make use of this abnormal retinal input plays a critical role in whether some functional vision is successfully restored or not. This review discusses plasticity in cortical and perceptual mechanisms within and beyond the primary visual cortex (V1) after years of blindness and asks: to what extent will this plasticity allow the human visual system learn to compensate for the distorted input provided by sight recovery technologies?

Previous experience with cochlear implants suggests that cortical plasticity is capable of successfully compensating for significant reductions and distortions of the sensory input. Although current cochlear implants generate severely degraded auditory input, extensive practice over the course of hours to approximately a year usually results in surprisingly good speech recognition in most adult-deafened cochlear implant recipients (Shannon 2012). However, although powerful, auditory cortical plasticity is not infinite and cannot compensate for distortions or loss of information that is too severe. For example, the earliest cochlear implants did not provide sufficient information to allow for speech perception (Eisen 2003).

The extraordinary ability of the auditory system to compensate for distortions inherent in cochlear implants has given the retinal prosthesis community hope that the visual system might show similar adaptive capacities in dealing with the distortions generated from retinal implants. Certainly, as discussed in the present review, human visual cortex is capable of experience-dependent cortical plasticity throughout the lifespan. However, in contrast to auditory cortex, plasticity at early stages of the visual hierarchy might be restricted. As described in more detail below, the preponderance of evidence suggests that large-scale cortical reorganization at the level of V1 may be very limited. This lack of plasticity early in the visual processing stream has important implications for what expectations are reasonable when hoping that patients can learn to interpret the input from visual prosthetics.

The goal of the present review is to briefly summarize the vast basic science literature on developmental and adult cortical plasticity with an emphasis on how this literature might relate to the field of sight recovery. Because we assume that most sight recovery technologies will be implanted in late blind individuals suffering from binocular loss (at least in the foreseeable future) certain important fields in the cortical plasticity literature are neglected in this review, including the effects of monocular deprivation (for reviews see Levi et al. 2015, Kiorpes 2016) and the development of cross-modal plasticity that occurs within congenitally blind individuals (for review see, Bavelier and Neville 2002, Lewis and Fine 2011).

We begin with formal definitions of cortical plasticity and perceptual learning. We then describe what is known, and what is unknown, about visual plasticity across the hierarchy of brain regions involved in visual processing, and across different stages of life. We close by discussing what is known about brain plasticity in sight restoration patients and discuss biological mechanisms that could be harnessed in future technologies to improve perceptual learning paradigms for these patients.

3. CORTICAL PLASTICITY AND PERCEPTUAL LEARNING: TWO SIDES OF THE SAME COIN

Cortical plasticity (also known as neuroplasticity) is an umbrella term that describes the ability of the brain to change its structure or function in response to experience. Cortical plasticity can be observed at multiple temporal scales, ranging from short-term: seconds to minutes to long-term: days to many months (Horton et al. 2017). Cortical plasticity also occurs across a wide range of spatial scales, ranging from alterations in the tuning characteristics of individual neurons up to reorganization of entire neuronal circuits ("cortical remapping", see Wandell and Smirnakis 2009, for a review).

The behavioral manifestation of cortical plasticity is *perceptual learning*. In a traditional perceptual learning paradigm, training on a specific task leads to a long-lasting improvement in behavioral performance (Karmarkar and Dan 2006, Deveau et al. 2014), such as a decrease in the minimal orientation difference that can be detected, or an increase in the speed for detecting target shapes embedded in distracters (for a review, see Sagi 2011). Similar to cortical plasticity, perceptual learning is a well-described feature of mammalian visual systems that occurs over multiple time scales – ranging from seconds (Mooney 1957) and minutes to years (Krupinski et al. 2013).

Although perceptual learning and cortical plasticity represent behavioral and physiological measurements of the same phenomenon, it has often proved difficult to understand the relationship between them. One reason for this is that performance improvements for apparently quite similar tasks can be mediated by very different cortical substrates. For example, training in auditory (Recanzone et al. 1993) or tactile (Recanzone et al. 1992a, Recanzone et al. 1992b, Recanzone et al. 1992c) frequency discrimination seems to result in "cortical recruitment" within primary sensory areas; that is, expansion of the amount of cortical territory/number of neurons representing the trained frequencies. In contrast, training on visual orientation discrimination tasks does not seem to substantially alter the topography of primary visual cortex (V1), or orientation selectivity of neurons in V1 (Crist et al. 2001, Ghose et al. 2002; though see Schoups et al. 2001 for evidence of subtle changes in tuning). Rather, visual perceptual learning is linked

to alterations in extra-classical contextual responses (Crist et al. 2001, Li et al. 2004), possibly mediated by altered response properties within V4 neurons with orientation tuning relevant to the task (Yang and Maunsell 2004).

4. PERCEPTUAL LEARNING

4.1.1 Learning as a function of stimulus complexity

As shown in Figure 2, the speed and extent of learning varies dramatically across different kinds of tasks or stimuli. Whereas it is possible to produce significant improvements in performance for tasks performed on basic attributes of a stimulus, such as grating detection, such effects tend to require very extensive training over up to tens of thousands of trials over many weeks (e.g. Li et al. 2008, Yehezkel et al. 2016). Similarly, perceptual learning for properties that are represented in V1, such as orientation tuning (Fine and Jacobs 2000) and contrast discrimination (Dorais and Sagi 1997, Adini et al. 2002, Yu et al. 2004), Landolt C acuity and two-line resolution thresholds tend to improve relatively slowly with practice. In contrast, learning for more complex higher-order properties, including discriminations that that are dependent on context (such as three-line bisection, Vernier discrimination, texture discrimination, contour detection, and shape discrimination) seem to occur more rapidly, with a few sessions and several hundred trials of practice (Fine and Jacobs 2000).

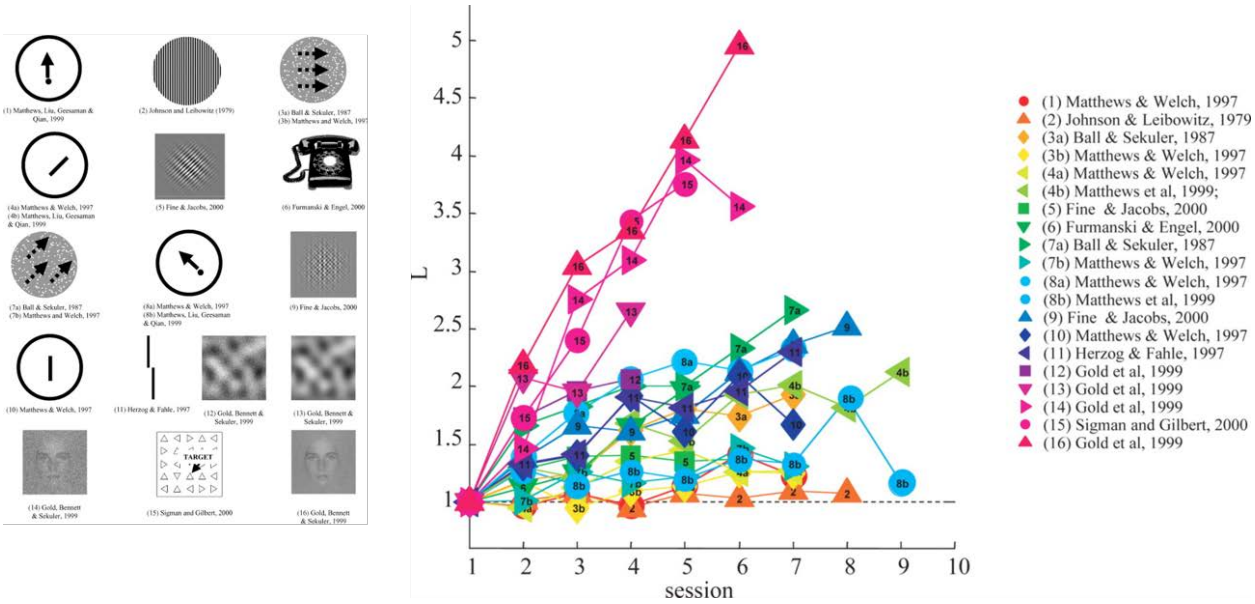

Figure 1: Learning as a function of session for 16 tasks. The task order roughly represents task complexity. For all studies performance on each session was converted into d' (Green and Swets 1966). The learning index, L, measures improvements in performance with practice, $L_s = d'_s/d'_1$, where s is the session number. A learning index remaining near 1 implies that observers showed no improvement in performance with practice. Reprinted with permission (Fine and Jacobs 2002).

One possible explanation for larger learning effects in more complex tasks is that low level representations may, by design, be resistant to plasticity in adulthood. Another possibility is that the larger amount of perceptual learning observed for complex tasks or stimuli may reflect the cumulative effects of changes in tuning properties across the visual processing cascade. Both possibilities are discussed in more detail below.

4.1.2 Generalization and specificity in perceptual learning

Since the goal of training with prosthetic stimulation will be to improve visual performance in a wider context than the laboratory, one important aspect of perceptual learning to consider is its specificity; that is, the degree to which improvements in performance generalize to untrained stimuli or tasks. In general, the transfer of learning from one task to another only occurs when the two tasks share cognitive elements (Woodworth and Thorndike 1901). Improvement in difficult tasks (Ahissar and Hochstein 1997, Talluri et al. 2015), and/or tasks involving simple features, such as contrast detection (Swift and Smith 1983) or discrimination (Dorais and Sagi 1997, Yu et al. 2004) tend to be highly specific. Improvements fail to generalize to untrained tasks performed with the same stimuli, or within the same task to untrained spatial frequencies, orientations, retinal locations, contrasts, or even eye of origin. Learning is also heavily disrupted by stimulus variability/uncertainty. For example, improvement in discriminating different contrast levels is disrupted if baseline contrasts are randomly interleaved (Adini et al. 2004, Yu et al. 2004). However, as shown in Figure 3, specificity in learning for properties like orientation or spatial location does not necessarily imply that learning occurs within early cortical regions, where contrast, orientation, and spatial invariance has not yet been achieved. Rather, the learning process may involve the retuning of higher-level neurons to become more specific for these properties (Mollon and Danilova 1996).

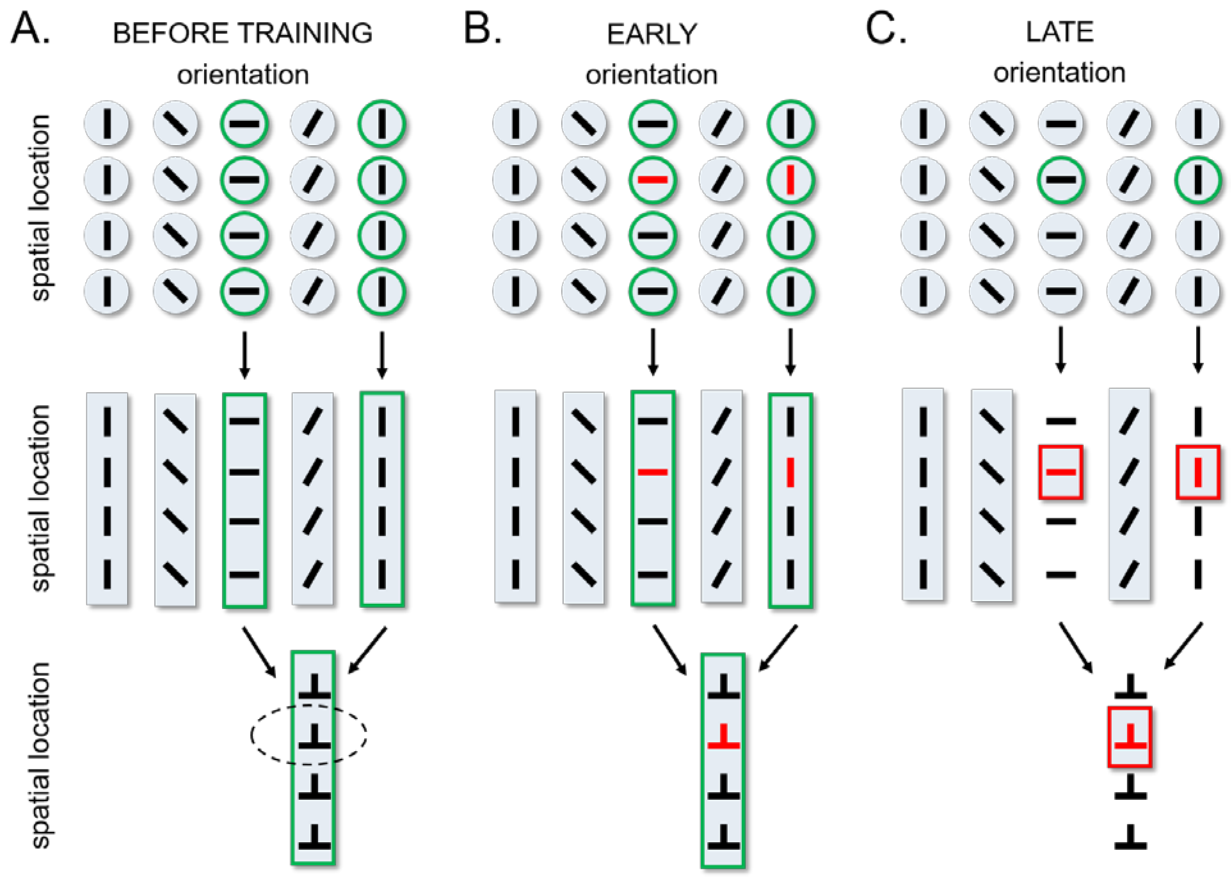

Figure 2. Schematic representation of how selective perceptual learning can occur. (A) A hierarchy of cortical areas progressively processes visual information. The first stages of processing tend to be highly specific for features, selective for both (for example) orientation and spatial location (e.g. simple cells). Intermediate stages in the hierarchy might combine specific early stage mechanisms (shown in green) to generalize over spatial location but remain specific for orientation (complex cells). Later in the hierarchy orientation features might be combined to form the initial stages of 3D shape processing (e.g. T-junctions). Here we compare two possible ways specificity in perceptual learning for spatial location might occur after training on a T-junction task at a specific spatial location (dashed circle). (B) In the 'early' model of perceptual learning performance improvement is mediated by tuning changes within early-stage mechanisms that are themselves tuned for spatial location and orientation (shown in red). Although 'read-out' occurs within higher-level mechanisms that generalize across spatial location, enhancement of performance due to training will be selective for spatial location. (C) In the 'late' model there is no effect of learning within low level mechanisms. Instead, spatially selective learning is the result of higher-level mechanisms becoming more selective for spatial location, due to reweighting, so as to become more spatially selective.

The limited and highly specific perceptual plasticity observed for low level features such as contrast or orientation has important implications for visual prosthetic design. Indeed, patients implanted with retinal prostheses show barely any improvement on simple perceptual tasks, such as contrast sensitivity (Castaldi

et al. 2016) or motion discrimination (Dorn et al. 2013, Castaldi et al. 2016) even after extensive training over several months.

Electronic prostheses have been shown to be fairly limited in the number of luminance levels that can be discriminated (Greenwald et al. 2009, Stingl et al. 2015) and current optogenetic sight recovery technologies are similarly expected to have a limited dynamic range for luminance (Gaub et al. 2015, Sengupta et al. 2016). In both technologies, sensitivity to contrast is also likely to be compromised by the absence of light/dark adaptation mechanisms within the photoreceptors and the horizontal cells (Bownds and Arshavsky 1995). The psychophysical literature described above suggests that it would be overly optimistic to expect patients to show improved sensitivity to these properties because of experience or training, except under highly specific contexts unlikely to be of much use in real world vision

With more complex tasks, making the task easier (Ahissar and Hochstein 1997, Talluri et al. 2015) produces less specific learning. In the absence of stimulus variability, learning remains highly specific – learning will generally occur at the most specific level possible (Ahissar and Hochstein 2004). But under conditions where stimuli are variable (e.g., presented at multiple spatial locations (Xiao et al. 2008, Wang et al. 2012, Wang et al. 2014), or with multiple different exemplars (Baeck et al. 2016), generalized learning can occur.

One important observation for sight recovery is that real-world tasks that require higher level representations, such as object recognition, might not require compensation for the distortions of sight recovery to occur at the earliest stages of processing (V1). For example, while it may be impossible to learn to see more brightness levels, it may be possible to develop higher level representations of objects that are less susceptible to this loss of grayscale information. For example, training with two-tone (Mooney) faces improves face/non-face discrimination abilities (Latinus and Taylor 2005).

It has recently been discovered that learning, especially for more simple features that are normally resistant to generalizable learning, can be enhanced through “gamification”- embedding the task within a video game context (e.g. Li et al. 2011, Deveau et al. 2014). Gamification has been shown to improve perception, visuomotor coordination, spatial cognition, and attention; with effects remaining even two years after the end of intervention (Feng et al. 2007, Bavelier et al. 2010). The gaming context may be particularly effective for a number of reasons: perceptual training within a gaming context includes more varied context than standard experimental perceptual learning regimes, and might recruit top-down, attentional systems, possibly altering the excitatory/inhibitory balance to allow heightened plasticity

(Feng et al. 2007). Gamification may also be particularly effective at recruiting reward and attentional neuromodulators such as dopamine (Koepp et al. 1998) and acetylcholine (Bavelier et al. 2010, Rokem et al. 2010, Rokem and Silver 2013) since video games are undoubtedly more engaging than standard psychophysical lab experiments. Finally, asking subjects to perform a task that is intrinsically rewarding is more likely to be successful in engaging patients in self-guided training – thereby reducing the need for personalized rehabilitation therapy.

To summarize, the perceptual learning literature provides guidance on to develop effective training paradigms for sight recovery patients. Extensive training on fine discriminations on a restricted stimulus set may well lead to improvements on the particular stimuli/task, but these improvements are unlikely to generalize to untrained stimuli. In contrast, learning to make coarser discriminations using a broader stimulus set, especially in a "gamification" context, will have more potential for generating visual improvements that generalize outside of the training context.

5. CORTICAL PLASTICITY WITHIN THE CRITICAL PERIOD

5.1. V1 cortical plasticity

Early in postnatal development, many tuning properties within primary visual cortex are remarkably plastic. Visual experience plays an important role in shaping the formation of ocular dominance columns, the size and orientation of receptive fields, as well as spatial frequency, direction, and disparity tuning (Wiesel and Hubel 1963, Wiesel and Hubel 1965, Raviola and Wiesel 1978, Movshon and Van Sluyters 1981, Sherman and Spear 1982, Ackman and Crair 2014). In the extreme, in animal models, when visual inputs are redirected into the auditory thalamus, the auditory cortex remodels to process visual information (reviewed in Horng and Sur 2006).

In contrast to most other tuning properties, visual experience plays only a minor role in the development of retinotopic organization, which is primarily driven by molecular signaling (Huberman et al. 2008, Cang and Feldheim 2013). In the mouse, retinotopic organization persists in the absence of retinal waves, albeit with reduced precision (Grubb et al. 2003, McLaughlin et al. 2003, Cang et al. 2005). Similarly, in the macaque, adult-like connections between V1 and V2 are present before LGN axons reach layer IV (Coogan and Van Essen 1996), although further refinement occurs with the onset of visual experience (Barone et al. 1995, Batardiere et al. 2002, Baldwin et al. 2012).

When visual experience is disrupted in infancy, there seems to be only limited capacity for retinotopic modification. Rod monochromats virtually lack rod photoreceptor function and therefore have a retinal

scotoma within the all-cone foveola. In these individuals some of the part of V1 that normally responds to the foveola responds to rod-initiated signals originating from neighboring regions of the retina (Baseler et al. 2002), suggesting some reorganization, but this organization is limited in spatial extent, and may be mediated by an expansion of receptive fields rather than by a fundamental reorganization of the retinotopic map.

The predominance of molecular cues is also observable in individuals born without an optic chiasm or even with only one cortical hemisphere. Individuals with albinisms (Hoffmann et al. 2003, Hoffmann et al. 2012), FHONDA syndrome (Ahmadi et al. 2016) or born with one cortical hemisphere (Muckli et al. 2009) have a miswiring of the retinal-fugal projection. Because retinotopic organization is primarily determined by molecular cues rather than visual experience this miswiring results in overlapped cortical representations of left and right visual hemifields where each region of cortex represents two distant (mirror symmetric) locations in visual space (Hoffmann et al. 2003, Hoffmann et al. 2012).

5.2. Plasticity beyond V1

In humans, there is a variety of evidence for remarkable flexibility in decoding congenitally abnormal representations within V1. For example, as described above, in individuals suffering from a miswiring of the retinal-fugal projection there is little or no compensation within V1. Despite this, acuity losses in these individuals are dominated by their foveal hypoplasia, and they show no perceptual confusion across mirror symmetric locations in the two visual hemifields (Bao et al. 2015). This suggests that a strikingly abnormal retinotopic organization within V1 can be successfully perceptually decoded by later stages of visual processing.

PD, an individual who had central cataracts resulting in annular pupils until the age of 43 similarly showed a host of perceptual adaptations to his distorted visual input, including suppression of diplopic images, and enhanced gain control for spatial frequencies that were heavily attenuated by his optics (Fine et al. 2002a).

Similarly, individuals with complete Schubert–Bornschein CSNB1 genetic deficits are thought to have severely compromised on-bipolar pathways (Cibis and Fitzgerald 2001, Bijveld et al. 2013). Yet these patients show surprisingly good visual performance under photopic conditions, with an average visual acuity of 0.3 logMAR (Zeitz et al. 2015) and report no perceptual difficulties beyond their acuity loss (M. Neitz 2015, personal communication).

In animal models, relatively few studies have examined the effects of congenital visual loss on higher levels of visual processing. However, as described above, when visual inputs are redirected into the auditory thalamus it not only elicits remodeling of the auditory cortex (reviewed in Horng and Sur 2006), but these responses can also guide simple visual behaviors, suggesting that visual information from auditory cortex can be integrated into the visual pathways (von Melchner et al. 2000).

6. ADULT PLASTICITY

6.1. V1 plasticity

Since the classic study of Wiesel and Hubel (1965) it has been clear that the plasticity of early visual areas declines sharply in adulthood. Kittens who had one eye sutured shut from birth until three months of age did not have functional vision in the closed eye, even after the eye had been reopened for a considerable period. This deterioration of functional vision did not occur in adult cats even when one eye was sewn shut for a year, showing that the effects of deprivation were far less extreme after the end of the critical period.

Curiously, tactile and auditory sensory areas may retain considerably more plasticity in adulthood. Both tactile (Recanzone et al. 1992a, Recanzone et al. 1992b) and auditory (Recanzone et al. 1993, Ohl and Scheich 2005, Polley et al. 2006) primary sensory areas have been demonstrated to show dramatic reorganization during adulthood. The reason for the relative lack of plasticity in V1 as compared to auditory or tactile sensory areas remains unclear. One possible explanation is that there significantly more subcortical processing within somatosensory and auditory pathways than within visual pathways. Thus, A1 and S1 can be considered as 'higher' in their processing pathways than V1 is within the visual processing hierarchy. If so, the lack of plasticity in V1 is consistent with the idea that plasticity increases across the sensory hierarchy (Hochstein and Ahissar 2002, Ahissar and Hochstein 2004), as discussed further below.

Two main types of experimental paradigms have been used to measure cortical plasticity in V1: training on feature-based tasks that vary in their complexity, and the effect of retinal lesions.

6.1.1 The effect of feature-based training on V1 responses

The most common task that has been used to assess adult V1 plasticity is orientation discrimination. While one monkey electrophysiology study found subtle changes in orientation tuning after several months of practice on an orientation discrimination task (Schoups et al. 2001), this result was not replicated by Ghose

et al. (2002) using a very similar paradigm. Electrophysiology studies using more complex tasks such as dot (Crist et al. 2001) or line bisection (Li et al. 2004) similarly did not find alterations in basic receptive field properties in V1, but did find that training altered top-down contextual influences.

One possibility is that effects of learning for orientation within V1 are predominantly due to contextual modulation of extra-classical receptive field properties of V1 responses (Gilbert et al. 2001) and/or modifications in feedback responses into V1 (Sagi 2011). This interpretation is consistent with the observations that (1) the effects of perceptual training on neuronal responses vanish when the trained task was not performed or when the monkey was anesthetized (Li et al. 2004), (2) experiments probing contextual effects, such as in contour integration, seem to display stronger effects than tasks like simple orientation discrimination (Gilbert et al. 2001), and (3) perceptual learning is tightly linked with attention (Crist et al. 2001).

Using fMRI BOLD responses, studies in human V1 have found evidence of some plasticity in adult visual cortex: enhanced responses to trained orientations have been found after training with a grating detection task (Furmanski et al. 2004) and an orientation texture discrimination task (Schwartz et al. 2002). Training in orientation discrimination also produced more discriminable cortical responses (Jehee et al. 2012). However, because of the sluggish hemodynamic response measured with BOLD imaging, it is not clear whether these alterations are driven by changes in bottom-up receptive field properties or top-down responses. While one EEG study (Pourtois et al. 2008) found that training *reduced* V1 responses (in contrast to these previous studies), starting as early as 40ms post-stimulus, this was an exploratory study that identified the time period of interest using relatively lax statistics that has yet to be replicated.

6.1.2 The effect of retinal scotomata on V1 responses

In animal models, several studies examining cortical responses after retinal lesions in cats and primates have reported that neurons in the lesion projection zone (LPZ) became responsive to stimulation of the retina surrounding the damaged area (Kaas et al. 1990, Gilbert and Wiesel 1992, Darian-Smith and Gilbert 1995, Abe et al. 2015) and show axonal sprouting (Darian-Smith and Gilbert 1994), consistent with large-scale retinotopic reorganization. However, other studies have failed to find evidence of retinotopic reorganization after retinal lesions (Rosa et al. 1995, Horton and Hocking 1998, Smirnakis et al. 2005). The discrepancy between reported outcomes from the above studies may be due to differences across laboratories in how the LPZ was measured (also see Calford et al. 2005, Smirnakis et al. 2005, for alternative explanations). Studies that found retinal reorganization (Kaas et al. 1990, Gilbert and Wiesel 1992, Darian-Smith and Gilbert 1995, Abe et al. 2015) estimated the receptive fields of V1 neurons by

fitting a Gaussian function to the regions of space that elicited a response to a bar (or similar) stimulus, both before and after the lesion. But the model used to estimate the receptive field location did not consider the absence of input when the stimulus was in the scotoma. Failing to factor in the absence of input when the stimulus falls within the scotoma biases receptive field estimates in a way that closely mimics the expected effects of cortical reorganization (Binda et al. 2013, Haak et al. 2015). In a second potential confound, non-spatially selective transient responses (as observed by Smirnakis et al. 2005) to the onset of a stimulus that is localized in space and time (i.e., a drifting bar) can easily bias the estimated receptive field location towards the location of the stimulus at the time of the transient response. In contrast, studies that failed to find retinotopic reorganization used methods that are robust to these confounds, such as measuring which regions of cortex remain silent in response to a full-field flicker stimulus (Smirnakis et al. 2005) or looking for evidence of recovery of responses in silenced cells (Rosa et al. 1995, Horton and Hocking 1998).

In humans, although BOLD studies have shown cortical fMRI retinotopic responses within the lesion projection zone in individuals with adult-onset scotoma (Baker et al. 2005, Baker et al. 2008, Dilks et al. 2009), these responses seem to be the result of strengthened top-down connections, rather than alterations in basic receptive field properties (Baseler et al. 2011), since cortical responses within the cortical region corresponding to the scotoma are reduced or eliminated by the withdrawal of attention (Masuda et al. 2008, Masuda et al. 2010).

6.2. Plasticity beyond V1

6.2.1 The effects of training or altered visual experience

Basic tuning tuning properties in higher-order areas of the visual cortex in adult animals seem to be more malleable with training than those in V1. For example, orientation tuning in V4 does change after training in an orientation discrimination task (Yang and Maunsell 2004). Analogous shaping of neuronal tuning to match task demands has also been found for more complex stimuli within primate inferotemporal (IT) cortex, the highest level in the ventral visual stream. When trained with shape stimuli that varied across four features, an enhanced neuronal representation was found for features that were important for the categorization task, relative to features that were irrelevant to the task (Sigala and Logothetis 2002). Similarly, training monkeys to discriminate novel visual stimuli causes the emergence of a population of IT neurons which respond selectively to these novel stimuli (Kobatake et al. 1998, DiCarlo and Maunsell 2000), or which become capable of distinguishing between them (Jagadeesh et al. 2001).

In human, the effects of altered visual experience on higher-level vision comes from case-studies of patients that have had their sight 'restored' after prolonged vision loss, either by ophthalmological procedures (including cataract (Fine et al. 2002b, Ostrovsky et al. 2009, Sinha et al. 2013, McKyton et al. 2015) or corneal replacement surgery (Fine et al. 2003b, Sikl et al. 2013). Improvements in the contrast sensitivity function has been noted in several (though not all) individuals who had sight restored at a young age (between the ages of 8-17 years) (Kalia et al. 2014). This ability to show learning for the contrast sensitivity function may be age–dependent: improvements were not noted in MM (Fine et al. 2003a) or PD (Fine et al. 2002a, a case of recovery from low vision), both individuals who had their sight restored in their 40s.

Impairments in shape processing, object recognition, and face processing are also observed in sight recovery patients, and these persist even after more than a decade of restored optical sight (Huber et al. 2015). Interestingly these deficits are observable both in individuals who have sight restored in late childhood (Sinha et al. 2013) and in a patient, KP, who lost vision at 17, and had his sight restored at age 71 (Sikl et al. 2013). Thus, the sensitive period for deprivation appears to be broader (extending to at least well into the teenage years) than the critical period for recovering normal vision. Interestingly, motion processing, including shape from motion, seems to be relatively robust to the effects of prolonged visual deprivation (Fine et al. 2003b, Saenz et al. 2008). In individuals who have suffered from prolonged blindness, visual prosthetics may prove to be more effective in providing input that can mediate 'dorsal-stream' tasks such as navigation (which are also less reliant on higher spatial frequencies), than 'ventral-stream' tasks such as reading, face recognition or object recognition.

6.2.2 Can higher-level visual areas compensate for V1 distortions?

Only one study has specifically examined flexibility in accessing patterns of activity with V1. Ni and Maunsell (2010) examined the effect of prolonged training on macaque detection thresholds for microstimulation within V1. Microstimulation thresholds decreased with training, and this training interfered with performance for detecting visual stimuli in the same cortical location, indicating that the local circuitry (whether within V1 itself, or within a higher cortical area decoding V1 activity) had somehow reconfigured to better detect behaviorally relevant patterns of neuronal activity.

In humans, a common example of an adult-onset distortion of V1 representations is macular degeneration. One of the first symptoms of this disease (earlier even than the presence of a noticeable blind spot), is visual distortion. Typically, straight lines appear wavy or crooked or the aspect ratio of objects is distorted (Gerrits and Timmerman 1969, Kapadia et al. 1994, Safran et al. 1999, Safran et al.

2000, Zur and Ullman 2003, Dilks et al. 2007, Mavrakanas et al. 2009). One likely explanation for these perceptual distortions is that shifts or expansions in receptive field properties within early visual areas such as V1 are not fully compensated for in later decoding (Dilks et al. 2007).

Perhaps the most extreme example of higher visual areas compensating for V1 distortion might be circumstances where V1 is absent. In monkeys, visual training after V1 lesions restores the ability to detect and localize visual stimuli in the blind fields (Weiskrantz and Cowey 1963, Mohler and Wurtz 1977). In humans, visual restoration therapy after V1 damage can restore some conscious vision, though the practical utility of this restored vision is yet to be established (for reviews see Pambakian and Kennard 1997, Melnick et al. 2016).

In summary, although higher level areas do seem to compensate for adult-onset distortions in V1, these abilities seem to be limited. One possibility is that there may be less flexibility in decoding the representation of retinotopic organization than there is for features that are more heavily influenced by developmental visual experience, such as disparity, direction and orientation tuning.

6.3. Why does plasticity vary across the visual hierarchy?

There are many possible reasons why the extent of cortical plasticity might vary across the hierarchy. One possibility is that this simply reflects the cumulative effects of plasticity at multiple preceding processing stages. Learning at each stage of processing presumably involves a selective reweighting of the connections from neurons that feed into that stage, with neurons best tuned for optimal performance given more weight (Saarinen and Levi 1995, Dosher and Lu 1998, Fine and Jacobs 2000). Given that the reweighting of neurons at each stage in the hierarchy presumably propagates to the next stage (and likely also influences lower stages due to cortical feedback) an increase in plasticity as a function of the number of preceding stages is not surprising.

A second, non-exclusive, possibility is that synaptic plasticity may genuinely vary across the visual hierarchy. There are a number of reasons why representations within early stages of visual processing may, by necessity, be resistant to plasticity in adulthood. For example, the representational demands of early visual cortex are unlikely to change substantially across the lifespan. Early visual areas represent the entire feature space (e.g. all orientations and spatial locations), although the sampling of that feature space is heavily dependent on childhood experience. Because this representation is complete and the low-level statistics of the environment do not change dramatically over the lifespan (i.e. we don't suddenly

experience new orientations in the same way as we experience new faces), there is little need for adult plasticity.

Indeed, allowing adult plasticity at early stages of processing might be expected to have deleterious consequences within later stages in the visual processing hierarchy. Any change in an early representation requires compensatory changes within all downstream mechanisms, as illustrated in Figure 4. Given that many complex objects are only experienced relatively infrequently, this compensation would presumably have to occur pre-emptively to experiencing those objects. Currently, there is no known neurobiological mechanism that could explain how this compensation could occur.

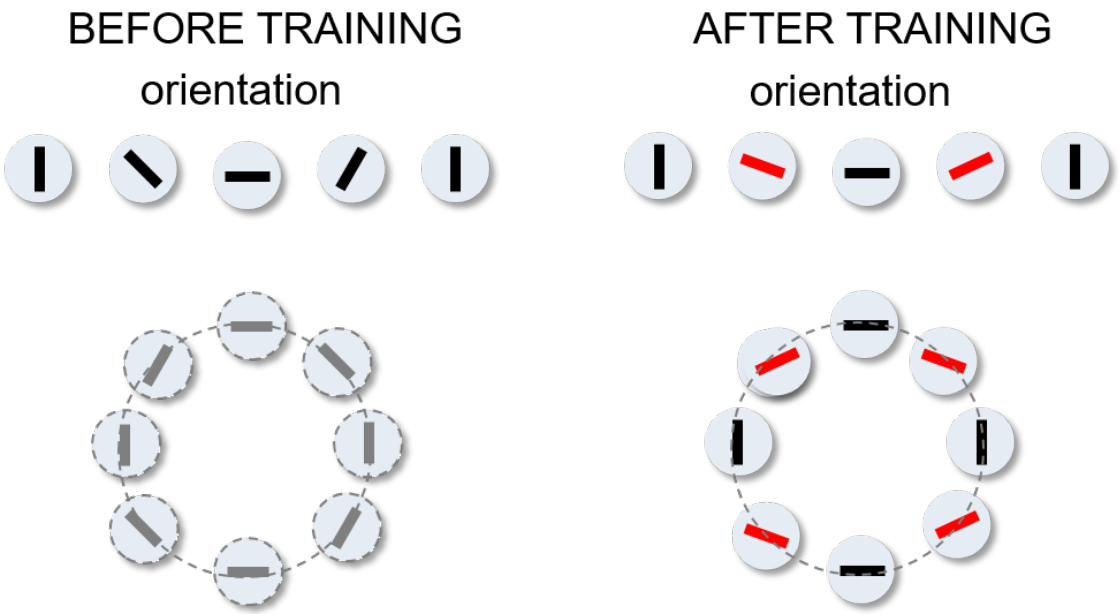

Figure 4. Any change in an early representation will distort downstream representations in the visual hierarchy unless those representations also change.

Finally, differences in plasticity across the cortical hierarchy may be the consequence of a qualitative differences in how information is represented. Early stage representations seem to reflect specific 'features' - for example, direct electrical stimulation of early visual cortex (V1/V2) elicits phosphenes (Tehovnik and Slocum 2007, Murphey et al. 2009). In contrast, electrical or TMS stimulation of areas like MT (Beckers and Homberg 1992), or IT/fusiform gyrus (Afraz et al. 2006, Rangarajan et al. 2014) can disrupt motion and face processing respectively, but does not elicit percepts (Murphey et al. 2009, Rangarajan et al. 2014). Representations in these higher-level areas may occur at a distributed network level (Levy et al. 2004) that may be more amenable to experience-dependent change.

7. EFFECTS OF TRAINING IN VISUAL PROSTHESIS PATIENTS

Sight recovery offers a unique platform to study cortical plasticity in adulthood. We have seen that local connections in adult cortex might be at least partially modifiable, but can such mechanisms support the learning that may be necessary to make sight restoration technologies useful?

Previous experience with cochlear implants would suggest optimism. Adult-implanted cochlear implant users initially report extremely unnatural and incomprehensible perceptual experiences. Over remarkably short time periods, not only do subjects become better at important tasks such as speech recognition, but their perceptual experiences become more qualitatively 'natural', as described by one patient: "It sounded like popcorn... every time someone said something it popped... as soon as I opened my mouth it popped… Now it sounds a little like Alice in Wonderland when she stands there in the tunnel talking. It is like more of a clanging sound now and it is very clear but still a bit lighter... more treble and like talking in a can." (Hallberg and Ringdahl 2004).

To date the effects of training on retinal prosthetics patients seem to have been relatively moderate. Although one study found decreases in detection thresholds as a function of time since surgery (Castaldi et al. 2016), the largest perceptual improvements have generally been reported in tasks such as moving independently in space, locating a large bright square on a screen, and identifying large-print letters ($\sim 40°$) at above-chance levels (Chader et al. 2009, Zrenner et al. 2011, Humayun et al. 2012, da Cruz et al. 2013, Dorn et al. 2013, Stingl et al. 2013, Rizzo et al. 2015). Single-letter recognition seems to take somewhere between a few seconds to three and a half minutes, enabling the best performing patients to read short words (da Cruz et al. 2013). In contrast, subject performance on relatively simple perceptual tasks, such as contrast sensitivity (Castaldi et al. 2016) and motion discrimination (Dorn et al. 2013, Castaldi et al. 2016), barely improved even after extensive training over several months. One possibility is that the perceptual 'experience' of prosthetic users will gradually improve over time, as seems to occur for cochlear implants, due to either a reduction in perceptual distortions or an increase in the perceptual discriminability of stimuli. Alternatively, improved performance in patients may be limited to use distorted information to perform specific tasks. This remains a topic that will require careful thought about how performance generalizes across tasks in future longitudinal studies of sight restoration patients.

Importantly, many assessments of the effects of training on visual prosthetic performance have focused on "closed" tasks under somewhat unrealistic contexts. This may lead to an overly optimistic assessment of performance or the effects of training. An example of a strongly closed task is "is that an 'A' or a 'B'".

An example of less closed task is “what letter is this?” An open task is “What is on the screen?” One issue with closed tasks is that, as described above, they are likely lead to perceptual learning that is specific to that particular context/task (see section 3.1 above). A second difficulty with closed tasks, particularly those that mimic open tasks, is that they can give a highly misleading impression of performance. As illustrated in 5A, when subjects are told that the four items on the able include a plate, a cup, a napkin and a fork it is easy to see how subjects can successfully ‘find the fork’. Real dinner tables tend to be more cluttered and disorganized. It is not clear that training to discriminate a fork among a preselected set of four items would generalize to finding a candlestick on a cluttered dinner table. The literature on perceptual learning, described above, indicates very strongly that learning will almost always occur at the most specific level possible given the training task. Thus, care should always be taken when designing training protocols to ensure that improvements are likely to generalize to performance outside the laboratory or clinic.

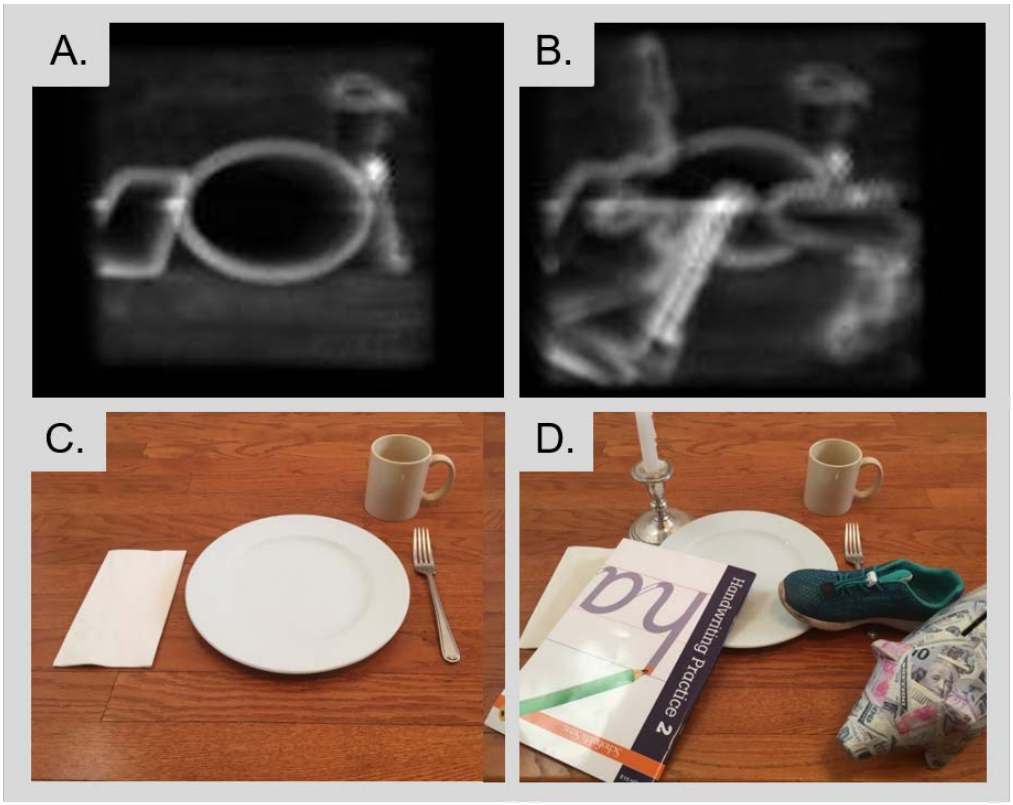

Figure 5. Two examples of a dining table under conditions of simulated prosthetic vision. Under ‘laboratory’ conditions the plate, cup, napkin and fork are easily differentiable. Real-world conditions for Dr. Fine’s dining table include multiple additional and unexpected objects. Finding the fork is challenging, even for an individual with normal vision.

8. REAWAKENING THE CRITICAL PERIOD

Recent advances in neurobiology have provided an increasingly detailed picture of the cascade of events that control critical period plasticity. Further understanding of these molecular mechanisms suggests ways in which pharmacological interventions could be used to facilitate plasticity in cases in which adult plasticity is limited. During early development, the synaptic neurochemical balance is shifted towards excitation, and synaptic connectivity is fluid. Synaptic rewiring includes physical pruning and homeostatic regrowth of synapses (controlled by the mediators tPA, TNFα, protein synthesis). Over time, responses to sensory input cause molecular triggers (e.g. orthodenticle homeobox 2, Otx2; BDNF) to promote inhibitory parvalbumin cell maturation and their increased GABA function. This shifts the excitation/inhibition balance towards a mature state of greater inhibition. The closure of the critical period is actively enforced by structural consolidation, including formation of a perineuronal extracellular matrix, and epigenetic brakes on plasticity (e.g., histone deacetylation) that silence the gene programs necessary for synaptic rewiring (Hensch 2005b, Bavelier et al. 2010, Takesian and Hensch 2013, Werker and Hensch 2015).

One important question is whether, in visual cortex, adult plasticity differs from juvenile plasticity quantitatively, or whether there are also qualitative differences (Karmarkar and Dan 2006). Specifically, it is not yet clear whether adult visual cortex can generate novel, functionally appropriate synaptic connections. Several studies have found that retinal lesions in the cat induce extremely rapid axonal sprouting and pruning over a longer timescale within of cortical neurons in the area corresponding to the scotoma (Darian-Smith and Gilbert 1994, Yamahachi et al. 2009, Marik et al. 2014). However, it is not clear whether this represents 'reawakening' of functional juvenile plasticity or more closely resembles the corruptive retinal remodeling that occurs in late stages of photoreceptor disease (Marc and Jones 2003).

One exciting avenue for improving prosthetic implant outcomes may come from harnessing new methods for 'reawakening the critical period' (Werker and Hensch 2015). Indeed Hensch and colleagues have demonstrated that cortical sensory plasticity can be successfully 'reawakened' via biochemical intervention in adult rodents (Hensch and Fagiolini 2005, Bavelier et al. 2010). FDA-approved cholinesterase inhibitors donepezil, galantamine and rivastigmine may shift the excitation/inhibition balance towards the 'immature' state of greater excitation. While shifting the neurochemical balance towards greater excitation may be necessary to 'reopen' the critical period, there is growing evidence that it is not sufficient (Hensch 2005a, Bavelier et al. 2010, Wong 2012, Takesian and Hensch 2013). Epigenetic brakes and structural limitations must also be overcome. As far as epigenetic limitations are concerned, it has been shown that valproate can reawaken plasticity by inhibiting histone deacetylases that silence

epigenetic limits on plasticity. In the retina, valproate provides restorative plasticity in both animal models (Osakada et al. 2007, Biermann et al. 2010) and retinitis pigmentosa patients (Clemson et al. 2011). In cortex, valproate has been successfully used to 'reopen' auditory cortex plasticity in adult humans (Gervain et al. 2013). As far as structural limitations are concerned, homeobox protein Otx2 may eventually serve a critical role in reawakening the critical period. Disruption of Otx2 reduces parvalbumin (thereby influencing excitatory/inhibitory balance) and reduces perineuronal net expression (thereby reducing structural limitations on plasticity). Disruption of Ox2 has proved sufficient to reopen plasticity in adult mice (Beurdeley et al. 2012, Spatazza et al. 2013).

9. Conclusions

Sight recovery technologies offer a unique platform for studying cortical plasticity in adults that is likely to increase in translational importance. The literature described in this review strongly suggests that there exists a "tolerance envelope" of adequate sensory information which any successful prosthetic device must match. If distortions or the amount of information loss fall within that envelope, it seems plausible that cortical plasticity can successfully compensate. However, it must be recognized that cortical plasticity is finite and cannot compensate for distortions or information loss that falls outside that envelope.

As the field of sight restoration progresses, it will become increasingly important to understand which visual distortions can be compensated for via cortical plasticity, which cannot, and what role training can play. Understanding the constraints imposed by cortical plasticity will be necessary if engineers are to develop technologies that fall within the sensory 'tolerance envelope'. Understanding what aspects of training can best facilitate visual learning will be critical for developing rehabilitation strategies that can efficiently help patients make best use of their implants.

This field of research will also yield fundamental insights within an important, but relatively poorly understood field of research – human adult plasticity. Perhaps the capacity that most differentiates humans from other animals is our capacity to continuously learn new perceptual and cognitive skills throughout our lives. Sight recovery patients are likely to provide a unique opportunity to gain insights into the fundamental principles that underlie these abilities.

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